

REMARKS

Status of Claims

Claims 1 and 3-22 are pending in the application. Claims 9-22 are withdrawn from consideration. Claims 1 and 3-8 are rejected.

Response to Rejection under 35 U.S.C. § 103

Claims 1 and 3-8 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Takada et al. (U.S. Patent No. 6,117,455) in view of Baker et al. (U.S. Patent No. 5,399,558).

Applicants respectfully traverse for the following reasons:

1. The Claimed Combination Of Two Anti-tuberculosis Drugs Is Non-Obvious In View Of The Cited References

The Examiner asserts that Takada discloses 1 nm - 10 µm particles comprising up to 90% drug and a polymer. Further, the Examiner states that Takada discloses anti-tuberculosis agents, specifically Isoniazid. The Examiner states that Baker discloses that Isoniazid and Rifabutin are known in the art to treat tuberculosis, and that suitable amounts are taught in the Physicians' Desk Reference. The Examiner asserts that the addition of Rifabutin disclosed by Baker to the composition taught by Takada to achieve a beneficial effect of a second anti-tuberculosis agent would have been obvious to one of ordinary skill. Further, the Examiner asserts that the determination of the particular ratio of drug to polymer and drug to drug may be achieved by routine experimentation.

In response to Applicants arguments regarding the insufficient motivation to combine Isoniazid and Rifabutin based on *In re Mills* as submitted in the Amendment filed on October 5,

2007, the Examiner further asserts that the submitted arguments are not applicable in this case as both drugs are used for the same treatment, thus providing the motivation for combining the two. The Examiner further states that the reference relied upon, *i.e.*, Sharma *et al.* (*Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis*. Pharm Res. 2001 Oct;18(10):1405-10), has not been supplied by Applicants.

Applicants respectfully submit that Sharma is discussed at paragraph [0023] of the present specification. Furthermore, Sharma is being submitted in an Information Disclosure Statement, concurrently with this Response.

Applicants further submit that in the last paragraph of the Introduction and the second paragraph of the Results and Discussion section of Sharma it is clearly stated that Isonazid and Rifampicin, when administered together, form an adduct which reduces the efficacy of the drugs. Therefore, a person of ordinary skill would not have been motivated to combine the two. Moreover, one of skill in the art would not have any reasonable expectation of success in combining the two, since Sharma indicates that the two may, in essence, cancel each other.

With regard to the criticality of the solvent ratio used in the present application, Applicants respectfully submit that methanol is a non-solvent for polylactic acid. Furthermore, methanol and dichloromethane are not miscible in all proportions, and a solvent system comprising the two is non-obvious, and therefore, the order of mixing to avoid precipitation is critical and non-obvious

2. The Claimed Ratios Of Drug(s) to Polymer and Of Drug to Drug Are Critical

The Examiner asserts that Applicants' arguments directed towards the unexpected results based on the combination of inhalation and oral routes do not overcome the previously set forth rejection because the present claims are directed particularly towards the composition of the anti-tubercular drug and not the method of administration.

Applicants respectfully submit that Takada's patent does not describe inhalation, but intranasal administration. The oral doses of different drugs do not accurately reflect the intracellular concentrations found in lung macrophages. Microparticles, however, ensure drug targeting in a particular ratio. This ratio is more beneficial for bactericidal activity, given the relative therapeutic indices of the drugs. Furthermore, the microparticles of the present invention are unusually high in drug content. Takada's 90% drug particles are neither inhalable, nor targeted, nor part of a controlled-release systems. Thus, high-payload microparticles capable of controlled-release, as in the present application, are non-obvious.

In view of the above, Applicants respectfully submit that claims 1 and 3-8 are patentable, and therefore request reconsideration and the withdrawal of the §103 rejection.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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